IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of
Yoshiko TAKAYAMA et al. : Group Art Unit: 1627
Serial No. 10/553,320 : Examiner: Gigi Georgiana HUANG
Filed: November 3, 2005 :
For: AGENT FOR REPAIRING
CORNEAL PERCEPTION

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, Yoshikuni NAKAMURA, the undersigned, a citizen of Japan residing at 5-1-23, Tenjin-cho, Suma-ku, Kobe-shi, Hyogo 654-0053 JAPAN do hereby declare and state:

That I am an employee of the Assignee of the above-identified application,

That I graduated from Osaka Kyoiku University with degree of Master of Education in March 1996,

That I was awarded a Ph.D. in Studies on Lens specific calpain in cataract formation from Gifu Pharmaceutical University in June 2000,

That I have been employed by Senju Pharmaceutical Co., Ltd., Osaka, Japan, since April 1996, and have been engaged in pharmaceutical research of said company,

That I am a member of Japanese Ophthalmological Society and published with other research workers, a number of reports on scientific studies, among others, including

(1) Nakamura Y, Sagara T, Seki K, Hirano S, Nishida T. Permissive effect of fibronectin on collagen gel contraction mediated by bovine trabecular meshwork cells. *Invest Ophthalmol Vis Sci.* 2003;44(10):4331-4336;

(2) Li Q, Fukuda K, Lu Y, Nakamura Y, Chikama T, Kumagai N, Nishida T. Enhancement by neutrophils of collagen degradation by corneal fibroblasts. *J Leukoc Biol.* 2003;74(3):412-419;

(3) Nakamura Y, Hirano S, Suzuki K, Seki K, Sagara T, Nishida T. Signaling mechanism of TGF-beta1-induced collagen contraction mediated by bovine trabecular meshwork cells. *Invest Ophthalmol Vis Sci.* 2002;43(11):3465-3472;

(4) Nakamura Y, Fukiage C, Shih M, Ma H, David LL, Azuma M, Shearer TR. Contribution of calpain Lp82-induced proteolysis to experimental cataractogenesis in mice. *Invest Ophthalmol Vis Sci.* 2000;41(6):1460-1466;

(5) Fukiage C, Azuma M, Nakamura Y, Tamada Y, Nakamura M, Shearer TR.

SJA6017, a newly synthesized peptide aldehyde inhibitor of calpain: amelioration of cataract in cultured rat lenses. *Biochim Biophys Acta.* 1997;1361(3):304-312;

That I am a co-inventor of the above-identified U.S. patent application Serial No. 10/553,320 and understand that this application has been rejected under 35 U.S.C. §103(a) as being unpatentable over Hellberg et al. (WO 03/020281) in view of McKerracher et al. (WO 99/23113) and Hara et al. (J. Neurosurg.(Spine 1) 2000;93:94-101),

That I believe the claimed subject-matter is not rendered obvious by the combination of the cited references, the reasons of which follow hereunder.

## 1. TRIGEMINAL (CORNEAL) NERVE IS DIFFERENT FROM OPTIC (RETINAL) NERVE

As described in Reference 1 ("Foundations of Neurobiology, Part 1, Chapter 3, pp. 68-71), *"whereas spinal nerves are all organized in the same pattern (dorsal roots being sensory, ventral roots being largely motor), not all cranial nerves are the same. Some are efferent, carrying motor information to muscles and glands; some are afferent, bringing sensory information into the brain; and some are mixed, carrying both efferent and afferent fibers."* (see page 69, right column, lines 6-14) Optic nerve, also called cranial nerve II, transmits visual information from retina to brain. The optic (retinal) nerve is composed of retinal ganglion cell axons and support cells. The axons of the optic nerve terminate in the lateral geniculate nucleus from where visual information is relayed to the visual cortex. Thus, the function of the optic nerve is visual perception and its destination is the lateral geniculate nucleus (see page 70, Table 3-3 and page71, Figure 3-14). In short, the optic nerve is a sensory nerve bringing sensory information into the brain. In contrast, trigeminal nerve also called cranial nerve V, which branches out into three nerves (ophthalmic (corneal) nerve, maxillary nerve and mandibular nerve), carrying not only sensory information in face such as cornea and conjunctiva of eye but also certain motor information. The three branches converge on the trigeminal ganglion and a single sensory root enters brainstem including mesencephalon, pons and medulla. Adjacent to the sensory root, a motor root emerges from the pons. Thus, the function of the trigeminal nerve is to carry sensory information from the face and control muscles that move the jaw, and the destination of the sensory root is mesencephalon, pons or medulla and the origin of the motor root is pons (see page 70, Table 3-13 and page71, Figure 3-14). In short, the trigeminal nerve is a mixed nerve carrying both sensory and motor fibers.

**Therefore, it is clear that the optic (retinal) nerve and the trigeminal (ophthalmic=corneal) nerve are entirely different from each other in their functions and structures.**

**In addition, as is clear from the difference in the functions, the corneal nerve and the optic (retinal) nerve are also different from each other in diseases/conditions caused by their injuries.** See, for example, Reference 2 (Levin and Albert eds., "Ocular

Disease; Mechanisms and Management"). In this reference, the diseases caused by corneal injury are described in SECTION 1, CAPTER 3, "Wound healing after laser in situ keratomileusis and photorefractive keratectomy", whereas those caused by retinal or optic nerve injury are described in SECTION 5, CAPTER 42, "Optic nerve axonal injury". Namely, the diseases/conditions caused by corneal nerve injury are considered to be entirely distinct from those caused by optic (retinal) nerve injury.

## 2. THERE IS NO CREDIBLE REASON TO PREDICT THAT Rho/ROCK SIGNAL TRANSDUCTION PATHWAY UNIVERSALLY REGULATES NEURITE OUTGROWTH OF ANY NERVES

Hellberg et al. teach that neurotrophic factor stimulators are useful in the treatment of dry eye and corneal nerve injury based on the common knowledge that neurotrophic factors such as NGF, BDNF, NT-3, bFGF etc. are important for the health and normal function of the cornea. Namely, Hellberg et al. merely teach that neurotrophic factor supply to corneal nerve cells is important for the neurite outgrowth and axonal elongation of the corneal nerve. **They fail to teach or suggest that Rho kinase (ROCK) signal transduction pathway is closely related to the neurite outgrowth inhibition of the corneal nerve.**

McKerracher et al. fail to remedy this deficiency of Hellberg et al.. The Examiner contends that McKerracher et al. teach that Rho antagonists (Rho inhibitors-e.g. C3) are effective agents for blocking myelin inhibition and stimulate axon growth and neurite outgrowth. However, they merely teach that Rho antagonists C3 and a dominant negative Rho, **rather than ROCK inhibitors**, are effective to stimulate neurite outgrowth of primary cerebellar granule neurons and/or retinal neurons. Rho antagosists block not only ROCK signal pathway but also signal pathways via other Rho effectors such as mDia, PKN, Rhophilin, Rhotekin and the like. **Therefore, one would not have a credible reason to replace Rho antagonists with ROCK inhibitors such as compounds claimed in claim 13 of this application.**

The deficiency of Hellberg et al. cannot be remedied by Hara et al. While Hara et al. teach that a ROCK inhibitor, fasudil hydrochloride, promotes neurological recovery after spinal cord injury (SCI) in rats, fasudil inhibits not only ROCK but also various protein kinase such as protein kinase C (PKC), myosin light chain kinase (MLCK), cAMP-dependent protein kinase and cGMP-dependent protein kinase. In fact, the authors suggest the involvement of PKC and MLCK (see "Discussion"). **Therefore, one could not expand or generalize the specified teaching of Hara et al. (i.e., fasudil) to other ROCK inhibitors including 4 specific compounds defined in claim 13.**

The Examiner contends that one would be motivated to utilize fasudil hydrochloride as a neurotrophic factor stimulator to treat dry eye or corneal nerve injury, even if he/she did not know the mode of action of fasudil, since Hara et al. teach that neurotrophic factors such as bFGF and NGF improve neurological recovery in SCI and McKerracher et al. teach that

Rho antagonists are neuron regenerators useful for peripheral nerve system (PNS) and central nerve system (CNS) conditions like SPI and retinal/optic nerve injury. **However, fasudil promotes neurite outgrowth by inhibiting ROCK signal pathway rather than increasing *in situ* production or activity of neurotrophic factors.** For example, in Reference 3 (J. Comp. Neurol. 2001;438:377-387) the authors discuss that in the absence of neurotrophic factors, activation or inactivation of one particular Rho GTPase may not be sufficient to change axonal outgrowth properties, suggesting that neurotrophic factor and Rho GTPase may affect to axonal outgrowth, independently. Therefore, one would not have a credible reason to combine Hellberg et al. and Hara et al.

In addition, McKerracher et al. fail to fill in the gap between Hellberg et al. that teach the recovery from corneal nerve injury and Hara et al. that teach the recovery from SPI. As mentioned above, cranial nerves are different from spinal nerves. Moreover, among the cranial nerves, the trigeminal (corneal) nerve and the optic (retinal) nerve are entirely different from each other in both their structures and functions (see Reference 1). Although McKerracher et al. may teach that Rho antagonists are useful for neurite outgrowth of PNS and CNS, this does not suggest ROCK inhibitors can universally promote neurite growth of any nerves. In addition, retinal nerve and corneal nerve are structurally and functionally different from each other, while they are both located in the eye. **Therefore, one would not have a credible reason to combine Hellberg et al. and Hara et al., even if he/she took into account the teaching of McKerracher et al.**

Furthermore, Reference 3 (J. Comp. Neurol. 2001;438:377-387) demonstrates that NGF-induced axonal elongation of rat trigeminal nerve is inhibited by lysophosphatitic acid (LPA) (Fig. 5E) and facilitated by a dominant negative Rho (RhoDN). However, this reference also discloses that perturbations in Rho activity (LPA and RhoDN) do not change the direction of BDNF-induced axonal elongation of rat trigeminal nerve (Fig. 8D). The authors discuss that **in the absence of neurotrophic factors**, activation or inactivation of one particular Rho GTPase may **not be sufficient to change axonal outgrowth properties**.

**This indicates that one would not have a credible reason to predict that Rho/ROCK signal transduction pathway universally regulates neurite outgrowth in any nerves including trigeminal nerves.**

**We found that two ROCK isoforms (ROCK I and ROCK II) are present in trigeminal ganglion cells and corneal tissue for the first time** in this application (see Experimental Example 3), hypothesized that Rho/ROCK signal pathway inhibits neurite outgrowth and axonal elongation of trigeminal (corneal) nerve, examined the effects of C3 (Rho antagonist) and 4 ROCK inhibitors on neurite outgrowth and axonal elongation of trigeminal nerve to verify the hypothesis (see Experimental Examples 1 and 2), and **confirmed that the inhibition of Rho/ROCK signal pathway can promote trigeminal (corneal) neurite outgrowth and axonal elongation, so the claimed specific ROCK inhibitors are useful for the recovery of corneal sensitivity after corneal nerve injury and**

**the treatment of dry eye associated with corneal hyposensitivity.**

The effects of the ROCK inhibitors on trigeminal (corneal) neurite outgrowth could not be predicted without our experiments disclosed in this application. Therefore, I consider that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning.

As discussed above, it would not have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize fasudil hydrochloride or the other claimed ROCK inhibitors in place of a neurotrophic factor stimulators in the method for treating dry eye or corneal nerve injury taught by Hellberg et al. in view of McKerracher et al. and Hara et al.

I further declare that all statements made herein of his knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 15th day of June, 2011.

Yoshikuni Nakamura

Yoshikuni NAKAMURA